# PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

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# PCT

## WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

Date of mailing
*(day/month/year)* see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

**FOR FURTHER ACTION**
See paragraph 2 below

| International application No. | International filing date *(day/month/year)* | Priority date *(day/month/year)* |
|---|---|---|
| PCT/US2004/022326 | 09.07.2004 | 10.07.2003 |

International Patent Classification (IPC) or both national classification and IPC
C07D401/12, C07D251/52, C07D251/54, C07D401/14, A61K31/506, A61K31/53, A61P17/02, A61P11/06,

Applicant
NEUROGEN CORPORATION

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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**WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2004/022326



**Box No. I Basis of the opinion**

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

**Box No. II Priority**

1. ☒ The following document has not been furnished:

   ☒ copy of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(a)).

   ☐ translation of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(b)).

   Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. ☐ It has not been possible to consider the validity of the priority claim because a copy of the priority document was not available to the ISA at the time that the search was conducted (Rule 17.1). This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

4. Additional observations, if necessary:

**Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 63-75, 80-101 and 106

because:

☒ the said international application, or the said claims Nos. 63-75, 80-101 and 106 with respect to industrial applicability relate to the following subject matter which does not require an international preliminary examination *(specify)*:

**see separate sheet**

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the whole application or for said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

| | | |
|---|---|---|
| the written form | ☐ | has not been furnished |
| | ☐ | does not comply with the standard |
| the computer readable form | ☐ | has not been furnished |
| | ☐ | does not comply with the standard |

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

**Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

| | | | |
|---|---|---|---|
| Novelty (N) | Yes: | Claims | 1-228 |
| | No: | Claims | |
| Inventive step (IS) | Yes: | Claims | 1-228 |
| | No: | Claims | |
| Industrial applicability (IA) | Yes: | Claims | 1-62, 76-79, 102-105, 107-228 |
| | No: | Claims | |

2. Citations and explanations

**see separate sheet**

**Box No. VIII Certain observations on the international application**

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

**see separate sheet**

**WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (SEPARATE SHEET)**

International application No.
PCT/US2004/022326



1) Reference is made to the following documents:

D1: WO 03/049702 A
D2: WO 02/08221 A

**2) Reference to section III**

Claims 63-75, 80-101 and 106 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

**3) Novelty (Reference to section V)**

Present compounds do not seem to have been disclosed in documents D1 and D2, which describe formulas being structurally close to derivatives of current claims 1, 18 and 38, but differing on the substitution pattern on the central piperazine ring.

Accordingly, the subject-matter of present claims 1-228 meets the requirements of Article 33(2) PCT.

**4) Inventive step (Reference to section V)**

D2, which may be considered to represent the closest state of the art, discloses diaryl piperazines, which are modulators of capsaicin receptors and are thus useful in the treatment of chronic and acute pain conditions, itch and urinary incontinence.
The compounds of D2 (cf. tables and examples in the description) differ from present ones in that a -N-C(=O)- or -N-C(=S)- group is linked to the piperazine moiety.
The problem to be solved by the present application may be regarded as the provision of further compounds which are modulators of capsaicin receptors (as disclosed in the application the terms "vanilliod receptor type 1" and "capsaicin receptor" are used interchangeably to refer to rat and/or human receptors of this type, as well as mammalian homologs).
D1 describes a wide number of compounds which are vanilloid receptor ligands, and some of them possess a sequence of 3 or 4 aromatic rings linked by an amine group, but they lack however the presence of a piperazine moiety.
Accordingly, it is deemed that the skilled person, even when considering to combine the

teaching of D1 with that of D2, would not have arrived at the subject-matter of present claims 1, 18 and 38.
Moreover, experimental data are given in the description for a reasonable and representative number of compounds, which indeed support the breadth of the claims.

Thus, the subject-matter of claims 1-228 meets the requirements of Article 33(3) PCT.

**5) Industrial applicability (Reference to section V)**

For the assessment of the present claims 63-75, 80-101 and 106 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

**6) Further observations (Reference to section VIII, Article 6 PCT)**

**6.1) Prodrug**: protection cannot be sought for speculative compounds, which have yet to be prepared and investigated. Although there is an indication within the application as to what it may be, a prodrug is not a definable term as regards its structure. The skilled person has no indication as to what falls within this definition, and it should thus be deleted. No analysis of novelty and inventive step has therefore been made for all the compounds which are combinations of "prodrug" and of derivatives of formulas of claims 1, 18 and 38.

**6.2)** Compound 42 on page 62 of the description does not seem to fall within the meaning of any of the formulas of claims 1, 18 and 38.

**6.3)** Although claims 112-228 have been drafted as separate independent claims, they appear to relate effectively to the same subject-matter and to fall within the meaning either of claims 1 or 18 or 38. The aforementioned claims therefore lack conciseness and as such do not meet the requirements of Article 6 PCT.

**6.4)** The description does not seem to be in line with the claims on file (cf. for instance pages 17, 20 and 24).

**6.5)** Claims 17, 37 and 57-60 do not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not clearly defined. The claims attempt to define the subject-matter in terms of the result to be achieved, which merely amounts to a statement of the underlying problem, without providing the technical features necessary for achieving this result.